

PATENT SPECIFICATION

(11) 1244798

1244798

NO DRAWINGS

- (21) Application No. 56580/69 (22) Filed 19 Nov. 1969
 (31) Convention Application No. P 18 11 654.6
 (32) Filed 29 Nov. 1968 in
 (33) Germany (DT)
 (45) Complete Specification published 2 Sept. 1971
 (51) International Classification C 07 d 49/36, 99/04, 99/06
 (52) Index at acceptance
 C2C 1G5A 1G5B 1G6B3 1Q11G 1Q1A 1Q6C 1Q7A 1Q8A
 5A4 5E2 B4A4 B4B B4C
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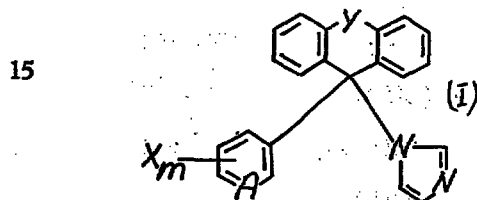


(54) N-SUBSTITUTED IMIDAZOLES AND THEIR SALTS

(71) We, FARBENFABRIKEN BAYER AK-
 TIENGESELLSCHAFT, a body corporate or-
 ganised under the laws of Germany, of Lever-
 kusen, Germany, do hereby declare the inven-
 5 tion, for which we pray that a patent may be
 granted to us, and the method by which it
 is to be performed, to be particularly described
 in and by the following statement:—

The present invention relates to certain new
 10 N-substituted imidazoles and salts thereof, to
 a process for their production and to the use
 thereof as pharmaceutical agents.

The present invention provides N-sub-
 stituted imidazoles of the general formula:—



in which

X is an alkyl or mercaptoalkyl radical or an
 electro-negative substituent,

Y is $-(CH_2)_n$, $-CH=CH-$, O or S,

A is nitrogen or CH,

m is 0, 1 or 2, and

n is 0, 1 or 2, as well as their salts.

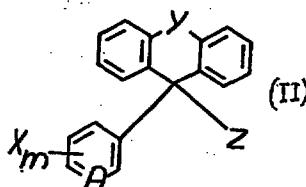
When X is an alkyl or mercaptoalkyl radical
 it preferably contains 1 to 4 carbon atoms.

25 When it is an electronegative substituent it
 may for example be halogen (fluorine, chlorine,
 bromine, iodine), or a nitro, cyano or trifluoro-
 methyl group.

30 When salts are to be used as pharmaceutical
 agents, they should of course be physiologi-
 cally compatible acceptable salts. Examples of
 acids giving such salts include the halogen
 hydracids, phosphoric acids, sulphonic acids,
 mono- and dicarboxylic acids and hydroxy-

carboxylic acids. There may be mentioned as
 examples of organic acids: acetic acid, maleic
 acid, succinic acid, tartaric acid, lactic acid,
 citric acid, salicylic acid, sorbic acid and naph-
 thalene-di-sulphonic acid-1,5. The salts with
 halogen hydracids (particularly hydrochloric
 acid), lactic acid and salicylic acid are of
 special interest.

The invention also provides a process for the
 production of the N-substituted imidazoles
 according to the invention in which a com-
 45 pound of the formula:—



in which X, Y, A and m of course have the
 above meanings, and Z is OH, chlorine or bro-
 mine is reacted (when Z is OH after a reaction
 with a halogenating agent to convert Z to
 chlorine or bromine), optionally in the pre-
 50 sence of an acid acceptor, with at least the
 theoretically required amount of imidazole in
 a polar solvent at 20 to 120°C.

The process is preferably carried out at 80
 to 100°C.

If the process is started from a compound
 in which Z is OH, then the halovenation may
 be carried out in an inert organic solvent, for
 60 example ether, petroleum ether, methylene
 chloride, benzene or toluene. All reagents
 suitable for the halogenation of tertiary al-
 cohols can be used as halogenating agents.
 There may be mentioned, by way of example:
 65 thionyl chloride, thionyl bromide, phosphoryl
 chloride, phosphoryl bromide, acetyl chloride
 and acetyl bromide. The halogenation is nor-
 mally effected within a temperature range of
 0 to 100°C, preferably 10 to 30°C, and after
 70

completion of the halogenation the solvent is replaced by a polar solvent. In some cases it may be advantageous to carry out the halogenation itself in a polar solvent directly followed, without intermediate isolation of the halide formed, by the reaction with the imidazole.

Examples of polar organic solvents include acetonitrile, nitromethane, acetone, diethyl ketone, dimethyl formamide or dimethyl sulfoxide.

In carrying out the reaction, the substituted methyl halide of formula (II) may be slowly added to a solution of the imidazole either in solution or in the solid form.

The reaction mixture may be worked up in conventional manner for example by con-

centrating or after diluting with water.

In a preferred method of carrying out the present process the starting compound (II) is reacted with the theoretically required amount of imidazole together with the theoretically required amount of an acid-acceptor. Suitable acid-acceptors include the usual organic bases, such as triethylamine, pyridine, dimethyl-benzylamine or alkyl-pyridine, and also inorganic compounds, for example alkali metal or alkaline earth metal carbonates.

Some of the new compounds which can be prepared by the methods of Examples 1-3 can be seen from Table I; in which the meanings of X, Y, A, and *m* in formula (I) are indicated for the various compounds. The sign "—" in the Y column denotes a direct bond.

TABLE I

	<i>m</i>	X	A	Y	m.p. °C.
(a)	0		CH	—	197—199
(b)	1	4—F	CH	—	156—159
(c)	1	4—Cl	CH	—	176—180
(d)	1	4—Br	CH	—	181—184
(e)	1	4—SCH ₃	CH	—	164—165
(f)	1	3—CF ₃	CH	—	134—138
(g)	1	3—Cl	CH	—	116—119
(h)	1	2—Cl	CH	—	156—158
(i)	0	H	CH	—(CH ₂) ₂ —	186—197
(k)	1	4—Cl	CH	—(CH ₂) ₂ —	216—218
(l)	1	4—F	CH	—(CH ₂) ₂ —	178—180
(m)	0		CH	—O—	160—162
(n)	0		CH	—S—	179—181
(o)	0		CH	CH=CH	208—211
(p)	1	4—F	CH	CH=CH	230—231
(q)	1	4—Cl	CH	CH=CH	231

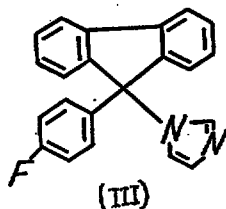
TABLE I (Continued)

	m	X	A	Y	m.p. °C.
(r)	1	4-Br	CH	CH-CH	
(s)	1	2-Cl	CH	CH=CH	210-215
(t)	1	3-CF ₃	CH	CH=CH	118-120
(u)	1	3-Cl	CH	CH=CH	199-201
(v)	1	3-CF ₃	CH	CH ₂ -CH ₂	115-118
(w)	0		3-N	—	80-85
(x)	0		3-N	CH ₂ -CH ₂	147-149
(y)	1	3-CF ₃	CH	CH ₂ -CH ₂	115-118
(z)	1	4-SCH ₃	CH	CH ₂ -CH ₂	180-183
(a)	1	2-CH ₃	CH	—	161-163

EXAMPLE 1

9 - (4 - fluorophenyl) - 9 - imidazolyl-fluorene

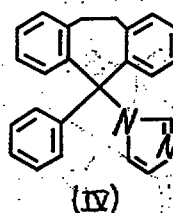
- 5 27.6 g (0.1 mol) 9 - (4 - fluorophenyl)-fluorene - 9 were dissolved in 250 ml dry methylene chloride and mixed at room temperature with 13.0 g (0.11 mol) thionyl chloride. The mixture was allowed to stand for 30 minutes, then boiled under reflux for 5 minutes and concentrated. The solid residue was washed with a little acetone and dried.
- 10 Portions of the 9 - (4 - fluorophenyl) - 9-chlorofluorene obtained in this way were introduced into a solution at 80°C of 20 g imidazole in 150 ml anhydrous acetonitrile. After 10 minutes the hot solution was filtered, concentrated and the residue mixed with water.
- 15 After suction-filtration and trituration of the residue with ether, 31 g of a yellowish crude product were obtained. Recrystallisation from ethanol yielded 118.0 g (55%) colourless crystals of the formula: —



m.p. 156-159°C

EXAMPLE 2

5 - phenyl - 5 - imidazolyl - [a,d]-dibenzocycloheptane

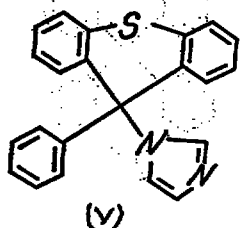


- 15.2 g (0.05 mol) 5 - phenyl - 5 - chloro-[a,d] - dibenzocycloheptane were added in portions to a boiling solution of 6.8 g (0.10 mol) dry imidazole in acetonitrile. The mixture was boiled for 10 minutes and then cooled to 0°C. After the addition of 100 ml ether, it was filtered off with suction. The residue was washed first with water and then with 100 ml ether. The combined ether filtrates were shaken out three times with portions of 200 ml water, then dried and concentrated. The residue was mixed with a little ethanol, cooled, filtered off with suction, washed with a little cold ether, combined with the filter residue first obtained, and dried. The total yield of the compound of the above formula: 13.1 g (78%); white leaflets of m.p. 186-187°C.

The starting compound was obtained as follows: 28.6 g (0.10 mol) 5-phenyl-5-hydroxy-[a,d]-dibenzocycloheptane were suspended in 100 ml dry methylene chloride and mixed with 13.8 g (0.12 mol) thionyl chloride. A vigorous SO₂ evolution started after a few minutes. The mixture was allowed to stand for 30 minutes, then boiled for 5 minutes and concentrated. The residue was recrystallised from light petrol. There were obtained 24.4 g (80%) 5-phenyl-5-chloro-[a,d]-dibenzocycloheptane of m.p. 115°C (decomposition).

EXAMPLE 3

10-phenyl-10-imidazolyl-thioxanthene 29.0 g (0.10 mol) 10-phenyl-10-hydroxy-thioxanthene were boiled for one hour with 40 g acetyl chloride in 100 ml dry petroleum ether (40/60). The clear solution was decanted from a small amount of an oily precipitate and concentrated. The residue was taken up with 200 ml dry acetonitrile and the mixture boiled under reflux for 3 hours with 13.6 g dry imidazole. The mixture was subsequently concentrated, the residue mixed with water, filtered off with suction and dried. The crude product was recrystallised from cyclohexane. Yield: 17.5 g (57%) 10-phenyl-10-imidazolyl-thioxanthene of m.p. 179—181°C.



The same results were achieved when the chlorides were replaced by bromides as starting compounds.

35 The free N-substituted imidazoles were converted into their salts in the usual manner, for example by heating in acetonitrile with somewhat more than the stoichiometrically re-

quired amount of the corresponding acid and subsequent isolation. The hydrochlorides are expediently obtained by passing in hydrogen chloride into the solution of the imidazole derivative, for example in carbon tetrachloride.

The following salts of the compounds (c), (e), (k) and (l) have the stated melting points:

fumarate	of (c):	182°C; (decomposition) starting at 90°C;
hydrochloride	of (e):	(decomposition) 186°C;
tartrate	of (k):	(decomposition)
salicylate	of (l):	137°C—138°C.

The new N-substituted imidazoles are valuable pharmaceutical agents. Their microbiological effectiveness can be seen from the description below.

In vitro on Sabouraud's Milieu d'Epreuve and in meat extract/glucose broth the new compounds exhibit a good fungistatic action against human-pathogenic fungi such as:

Trichophyton species, especially *Trich. ment.*, *Trich. rubrum*; *Epidermophyton floccosum*.
Microsporon species, especially *M. canis*, *M. felineum* and *M. audouinii*.
Candida species, especially *Candida albicans*.

Further gemmiparous fungi, especially *Cryptococci*, *Histoplasma* and *Coccidioides* species.

Aspergilles, especially *A. fumigatus*, *A. niger* and *A. nidulans*.
Penicillium species, especially *Pen. commune*.

Chromomycetes (*Hormodendrum* and *Phialophora* species).

The minimum inhibition concentrations against some of the above fungi are given in Table 2 (in which the compounds are the indicated compounds of Table 1).

TABLE 2

Compound	<i>Trichoph. ment.</i> and <i>Microsporon canis</i>		<i>Candida alb.</i>		<i>Asperg. niger</i>	Penicillin
	with serum	without serum	with serum	without serum		
(a)	<4γ	<4γ	10—4γ	<4γ	<4γ	<4γ
(b)	<4γ	<4γ	100γ	4—10γ	<4γ	<4γ
(c)	<4γ	<4γ	40γ	4γ	10γ	<4γ
(d)	<10γ	<4γ	20γ	<4γ	<4γ	4
(e)	<4γ	<4γ	100γ	10γ	100γ	100γ
(f)	<4γ	<4γ	20γ	<4γ	<4γ	<4γ
(g)	<4γ	<4γ	40γ	<4γ	4γ	<4γ
(h)	<4γ	<4γ	20γ	<4γ	<4γ	<4γ
(i)	<4γ	<4γ	40γ	<4γ	<4γ	<4γ
(k)	<4γ	<4γ	4γ	4γ	—	—
(l)	10γ	<4γ	100γ	<4γ	<4γ	10γ
(m)	>100γ	>100γ	100γ	20γ	—	100γ
(n)	>100γ	>100γ	40γ	40γ	—	100γ
(w)	<4γ	4γ	100γ	40γ	100γ	20γ
(v)	10γ	4γ	4γ	10γ	—	40γ
(x)	10γ	<4γ	10γ	10γ	—	40γ

In vivo, the preparations were therapeutically applied as follows.

(1) In an experiment carried out on white mice infected with *Candida*. When doses of 50—100 mg/kg body weight were orally given once or twice daily, more than 80% of the animals survived the infection, whereas 95—100% of the untreated infected control animals died due to the infection 6 days *p.i.* The compounds (a), (d) and (f) of Table 1 were especially effective in this experimental arrangement.

(2) In an experiment carried out on white mice infected with *Trichophyton quinckeanum*, the typical Quinckeanum dermatomycosis was treated with the compounds (a), (d) and (f) with 2 mg/mouse orally per day (100 mg/kg). The course of the dermatomycosis was substantially shortened by this therapy; in a prophylactic experiment the development of

the infection could be suppressed with the above-indicated dosage.

(3) When locally applied to guinea pigs infected with *Trich. ment* particularly, for example, the compounds (a), (f), (g) and (k), dissolved 1% in dimethyl sulphoxide/glycerol, have a good therapeutical action.

For humans the dosage amounts, on average, to about 20 to about 60 mg/kg body weight, preferably 30 to about 50 mg/kg body weight, given at intervals of up to 12 hours for a period of about 12 to about 20 days.

It may sometimes be necessary to deviate from the aforementioned quantities, depending for example on the method of application, the individual reaction to the medicament, its formulation, and the moment of time or interval at which it is administered. It may thus be sufficient in some cases to manage with less than the above-mentioned minimum amount;

whereas in other cases the indicated upper limit may have to be exceeded. If larger quantities are administered, it may be advisable to distribute these in several individual doses over the day.

The chemotherapeutic agents can be used as such or in combination with pharmaceutically acceptable carriers. Suitable forms of application, in combination with various inert carriers, are the following: tablets, capsules, powders, sprays, aqueous suspensions, injectable solutions, elixirs, syrups and the like. Such carriers comprise solid diluents (or fillers), a sterile aqueous medium, non-toxic organic solvents and the like. Tablets and the like intended for oral use may, of course, be provided with sweetening additives and similar substances. The therapeutically active compound should normally be present at a concentration of 0.5 to 90 per cent by weight of the total mixture, in quantities which are sufficient to achieve the range of dosage mentioned above.

For oral application, the tablets can obviously also contain additives, such as sodium nitrate, calcium carbonate and dicalcium phosphate together with various other additives, such as starch (preferably potato starch) and the like, and binding agents, such as polyvinylpyrrolidone, gelatin and the like. Lubricants, such as magnesium stearate, sodium lauryl sulphate and talc may also be used concurrently for the production of the tablets. In the case of aqueous suspensions and/or elixirs which are intended for oral use, the active substance may be provided with various agents improving the flavour, colouring substances, emulsifiers and/or other diluents, such as water, ethanol, propylene glycol, glycerol and similar compounds or combinations.

In the case of parenteral application, solutions of the active substances in sesame or peanut oil, or in aqueous propylene glycol or N,N - dimethyl formamide can be employed, as well as sterile aqueous solutions in the case of water-soluble compounds. Aqueous solutions of this kind should be buffered in usual manner if necessary; furthermore, the liquid diluent should be rendered isotonic from the start by the addition of the necessary amount of salt or glucose. Such aqueous solutions are particularly suitable for intravenous, intramuscular and intraperitoneal injections. Sterile aqueous media of this kind may be prepared in known manner.

For topical application (e.g. solutions, creams, ointments) preferably a concentration of about 0.5 to 10 per cent is used.

In the case of mice, rats, rabbits, dogs and cats the LD₅₀ of the above compounds ranges from about 500 to 900 mg/kg body weight when orally administered.

The invention therefore also provides a

pharmaceutical composition comprising at least one of the new active compounds in admixture with a solid or liquid diluent or carrier.

The invention further provides a medicament in dosage unit form comprising at least one of the new active compounds either alone or in admixture with a solid or liquid diluent or carrier. The medicament may include a protective envelope containing the active compound and, if used, the diluent or carrier.

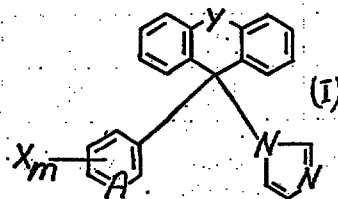
The term "medicament in dosage unit form" as used in the present specification means a medicament as defined above in the form of discrete portions each containing a unit dose, or a multiple or sub-multiple of a unit dose of the active compound or compounds. Such portions may, for example, be in monolithic coherent form, such as tablets, suppositories, pills or dragees; in wrapped or concealed form, such as wrapped powders, cachets, sachets, or capsules; in ampoules, either free or as a sterile solution suitable for parenteral injection; or in any other form known to the art.

Besides the antimycotic activity the compounds show an activity against pathogenic protozoa, e.g. *Trypanosoma*, *Trichomonas*, *Entamoeba histolytica*, malaria parasites, *Toxoplasma* and against viruses and bacteria, e.g. *Staphylococci*, *Streptococci*, *Klebsiella*, *E. coli*.

Further the compounds activate the granulation in wound healing and show a hypocholesterinaemic activity.

WHAT WE CLAIM IS:—

1. N - substituted imidazoles of the formula:—



in which

X in an alkyl or mercaptoalkyl radical or an electro-negative substituent,

Y is $-(CH_2)_n-$, $-CH=CH-$, O or S,

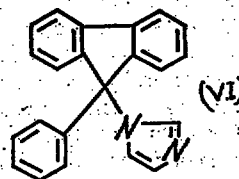
A is nitrogen or CH,

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2. The compounds herinbefore identified in Table 1 as (a) to (x).

3. The compounds of the formula:—



4. The compound of the formula:—



whereas in other cases the indicated upper limit may have to be exceeded. If larger quantities are administered, it may be advisable to distribute these in several individual doses over the day.

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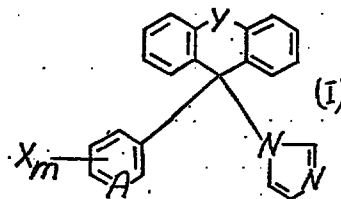
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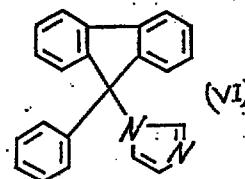
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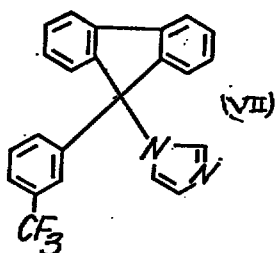
n is 0, 1 or 2, as well as their salts.

2. The compounds hereinbefore identified in Table 1 as (a) to (x).

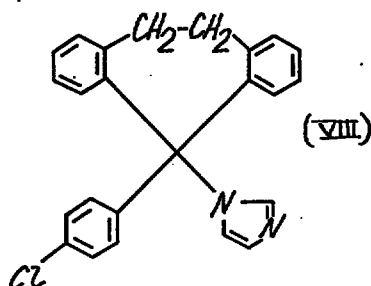
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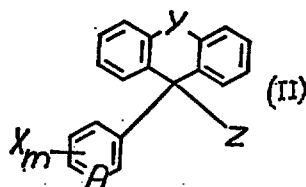


5. The compound of the formula:—



6. Pharmaceutically acceptable salts of a compound of formula (I) or according to any claims 2—5.

7. A process for the production of a compound according to any of claims 1—6 in which a compound of the formula:—



in which

Z is OH, chlorine or bromine,

is reacted, when Z is OH after a reaction with a halogenating agent to convert Z to chlorine or bromine, optionally in the presence of an acid acceptor, with at least the theoretically required amount of imidazole in a polar organic solvent at 20 to 120°C.

8. A process according to claim 7 in which the reaction with the imidazole is effected at 80 to 100°C.

9. A process according to claim 7 or 8 in

which the polar organic solvent is one of those hereinbefore mentioned.

10. A process according to any of claims 7—9 in which the compound of formula (II) is slowly added to a solution of the imidazole.

11. A process according to any of claims 7—10 in which Z is OH and the halogenating agent is one of those hereinbefore mentioned.

12. A process according to any of claims 7—11 in which Z is OH, in which the reaction with the halogenating agent is effected at 10 to 30°C.

13. A process for the production of a compound according to claim 1, substantially as hereinbefore described in any of the examples.

14. Compounds according to claim 1 whenever produced by a process according to any of claims 7—13.

15. A pharmaceutical composition comprising at least one compound according to any of claims 1—6 or 14 in admixture with a solid or liquid diluent or carrier.

16. A composition according to claim 15 containing 0.5 to 90% by weight of the compound or compounds.

17. The compounds hereinbefore identified in Table I as (y), (z) and (α).

18. A medicament in dosage unit form (as hereinbefore defined) comprising at least one compound according to any of claims 1—6, 14 or 17 either alone or in admixture with a solid or liquid diluent or carrier.

19. A chemotherapeutical solution for topical application, containing from 0.5 to 10 per cent of a compound according to any of claims 1—6 or 14 as effective ingredient.

20. A chemotherapeutical cream for topical application containing from 0.5 to 10 per cent of a compound according to any of claims 1—6 or 14 as effective ingredient.

21. A chemotherapeutical ointment for topical application containing from 0.5 to 10 per cent of a compound according to any of claims 1—6 or 14 as effective ingredient.

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